Scientific Abstract

This multicenter, open-label, dose-escalating gene therapy clinical study will evaluate the effects of several dose levels of intramyocardial pVGI.1(VEGF2) plasmid deoxyribonucleic acid (DNA) with respect to safety and efficacy in patients with stable exertional angina despite medical therapy. The pVGI.1(VEGF2) plasmid contains the complementary DNA sequence for the vascular endothelial growth factor 2 protein, a member of a class of natural growth factors that promote angiogenesis. This study will obtain information regarding the safety, duration of activity, and optimal dose of this gene for the relief of angina.

The primary objectives of the study are as follows:

- To assess in adult patients with refractory and stable exertional angina the effects of single, defined increasing doses of pVGI.1(VEGF2) given by direct intramyocardial injection on safety as determined by frequency, severity, and duration of treatment-emergent adverse effects

- To assess in adult patients with refractory and stable exertional angina the effects of single, defined increasing doses of pVGI.1(VEGF2) given by direct intramyocardial injection on change in angina class and exercise tolerance at 12 weeks after dosing when compared with pretreatment assessments

A secondary objective of the study will be to correlate the changes in angina class and exercise tolerance with changes in myocardial perfusion assessed by myocardial scintigraphy.

Key inclusion criteria for this study are that patients are stable and not in a setting of life-threatening ischemia, have a history of functional Canadian Cardiovascular Society class 3 or 4 angina refractory to medical therapy, have areas of viable but underperfused myocardium demonstrable on a single photon emission computed tomography (SPECT) myocardial perfusion study (technetium-99m with stress and rest), and have multivessel occlusive-coronary-artery disease and/or occlusion of one or more coronary artery bypass grafts. Key exclusion criteria for this study are that patients do not have a history of clinically successful coronary artery bypass graft surgery, angioplasty, or percutaneous myocardial revascularization/transmyocardial revascularization in the preceding 3 months, do not have other severe concurrent illnesses (*e.g.*, congestive heart failure or left ventricular ejection fraction less than 25%), do not have a history of neoplasm or active retinopathy, and are unable to undergo cardiac catheterization or nuclear testing.

This study will include 30 patients who will be enrolled sequentially into 3 dosing cohorts. Each cohort will consist of 10 patients. Three pVGI.1(VEGF2) dose levels will be used: 200, 800, and 2000 μg. The patient will receive the total dose by 4 intramyocardial injections into the ischemic regions of the myocardium by a minimally invasive thoracotomy.

All patients in a dosing cohort will be evaluated for safety prior to progressing to the next dosing cohort; therefore, dosing in successive cohorts will occur not less than 2 weeks apart. The study will consist of a Pretreatment Phase (up to 4 weeks), a Treatment Phase (1 day), and a Post-treatment Phase (12 weeks).

Safety will be assessed by recording physical examination findings, vital signs, 12-lead electrocardiogram, clinical laboratory test results, and adverse experiences at various intervals over a period of 12 weeks after treatment.

The effectiveness of treatment will be evaluated by assessing angina class, exercise tolerance, and perfusion defects using myocardial scintigraphy performed with SPECT (using the same protocol and isotope used at baseline) 12 weeks after treatment as compared with baseline assessments. After Week 12 Post-treatment Phase assessments have been completed, patients will be entered into a follow-up study to collect long-term safety and efficacy data.